UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,783	11/13/2001	Itamar Willner	10980-16001	8069

20985 7590 08/04/2006

FISH & RICHARDSON, PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,783	WILLNER ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-8,23-33 and 48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 48* is/are rejected.

7)☒ Claim(s) *4-8 and 23-33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on May 22, 2006 has been entered. The claims pending in this application are claims 1-8, 23-33, and 48. Rejections and/or objections not reiterated from the previous office action are hereby withdrawn in view of amendment filed on May 22, 2006.

Claim Objections

2. Claims 3 and 28 are objected to because of the following informality: "of about" should be "about".

3. Claim 3 is objected to because of the following informality: "the stably highly hybridizing portions of the capturing and verification oligonucleotides" should be "the stably hybridizing portions of the capturing and verification oligonucleotides" in order to correspond with claim 1.

4. Claims 8 and 33 are objected to because of the following informality: "one or more times" should be "for one or more times".

5. Claim 23 is objected to because of the following informality: "lipsome" should be "liposome".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. New Matter

Claim 48 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Although the specification describes "[A]s the oligonucleotide and oligonucleotide-DNA layered assemblies are negatively charged, the electrostatic repulsion of a negatively-charged redox-probe, e.g.Fe $(CN)_6^{3-/4-}$, from the electrode support is anticipated to perturb the interfacial electron transfer. This is expected to introduce an electron transfer resistance that can be detected by Faradaic impedance spectroscopy or other electrochemical means such as reduction of the amperometric response of the electrode" (see page 14, lines 3-12), this indicates that oligonucleotide and oligonucleotide-DNA layered assemblies introduce an electron transfer resistance by the electrostatic repulsion of a negatively-charged redox-probe, e.g.Fe $(CN)_6^{3-/4-}$. However, the specification fails to define or provide the limitation "the presence of the verification oligonucleotide on the sensing interface causes an increase in the insulation of the sensing interface to interfacial electron transfer between the sensing interface and the surrounding medium" as recited in claim 48.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of

the application as filed, the examiner should conclude that the claimed subject matter is not described in that application."

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1, 2, and 48 are rejected under 35 U.S.C. 102(e) as being anticipated by Blackburn *et al.,* (US Patent No.6,686,150, priority date: January 29, 1998).

Blackburn *et al.,* teach a method for detecting a target sequence in a sample comprising: a) providing a rolling circle probe (RCP) comprising: i) a first ligation sequence substantially complementary to a first domain of said target sequence; ii) a second ligation sequence substantially complementary to a second domain of said target sequence; and iii) a priming sequence; b) hybridizing said first ligation sequence to said first domain and said second ligation sequence to said second domain to form a first hybridization complex; c) ligating said first and second ligation sequences together; d) adding to said first hybridization complex: i) a primer substantially complementary to said priming sequence; ii) a polymerase; iii) dNTPs; and iv) an electron transfer moiety (ETM); to form a rolling circle concatamer comprising at least one covalently attached ETM; and e) detecting said ETM as an indicator of the presence of said target sequence wherein said RCP further comprises a third domain comprising a capture

sequence, and said method further comprises hybridizing said concatamer to a capture probe covalently attached to an electrode (see columns 141, claims 1 and 2).

Regarding claim 1, since Blackburn *et al.,* teach to make a rolling circle concatamer by hybridizing a RCP comprising a first ligation sequence and a capture sequence to a target sequence and the ligation and amplification reactions and hybridize said concatamer to a capture probe covalently attached to an electrode (see columns 141, claims 1 and 2), Blackburn *et al.,* disclose a sensor device (ie., an electrode) having a sensing interface carrying capturing oligonucleotides wherein each carrying capturing oligonucleotide has a nucleotide sequence (ie., multiple identical capture probes), a stably hybridizing portion of which is complementary to a first portion (ie., a capture sequence) of the target oligonucleotides (ie., RCP in said concatamer having RCP wherein RCP is the target oligonucleotide here) wherein said sensor device comprises an electrochemical probe carrying the sensing interface (ie., an electrode) and the probe is located in a surrounding medium (ie., the hybridization buffer) as recited in (a) of claim 1, providing verification oligonucleotides wherein each verification oligonucleotide has a nucleotide sequence (ie., multiple identical target nucleic acids), a stably hybridizing portion of which is complementary to a second portion of the target oligonucleotide (ie., a first ligation sequence of RCP), other than said first portion as recited in (b) of claim 1, contacting the sample (ie., said concatamer having RCP) with the sensing interface under conditions such as to allow the target oligonucleotides (ie., RCP in said concatamer) if present in the sample, to hybridize to the capturing oligonucleotides (ie., multiple identical capture probes on the electrode) as recited in (c) of claim 1, and prior to (c), allowing the verification oligonucleotides (ie., multiple identical target sequences) to hybridize to the target oligonucleotides (ie., RCP) if present in the

sample as recited in (d) of claim 1. Since Blackburn *et al.,* teach detecting said ETM as an indicator of the presence of said target sequence (see column 141, claim 1) and insulators (such as resistance) is used to monitor electron transfer between ETM and the electrode (see column 92, fourth paragraph), and the measurement of insulators (such as resistance) must be performed in or through the hybridization buffer (ie., having ETM), Blackburn *et al.,* disclose detecting the presence of said verification oligonucleotides (ie., the target sequence) on the sensing interface by measuring insulation of the sensing interface (ie., surface of the electrode) to interfacial electron transfer between the sensing interface and the surrounding medium (ie., the hybridization buffer containing ETM) as recited in (e) of claim 1.

Regarding claim 2, Blackburn *et al.,* teach that said detection is based on Faradaic impedance spectroscopy or amperometric measurements (see column 91, last paragraph and columns 92 and 96).

Regarding claim 48, since Blackburn *et al.,* teach providing verification oligonucleotides wherein each verification oligonucleotide has a nucleotide sequence (ie., multiple identical target nucleic acids), a stably hybridizing portion of which is complementary to a second portion of the target oligonucleotide (ie., a first ligation sequence of RCP), other than said first portion as recited in (b) of claim 1 (see above) and the target nucleic acids taught by Blackburn *et al.,* carries the negative charges and has the same properties of the verification oligonucleotides recited in claim 1 (the verification oligonucleotides with the same properties can perform the same functions), Blackburn *et al.,* disclose that the presence of the verification oligonucleotide on the sensing interface causes an increase in the insulation of the sensing interface to interfacial

electron transfer between the sensing interface and the surrounding medium as recited in claim 48.

Therefore, Blackburn *et al.*, teach all limitations recited in claims 1, 2, and 48.

Response to Arguments

I. In page 7, fourth paragraph bridging to page 10, third paragraph of applicant's remarks, applicant argues "the methods of Blackburn employ an oligonucleotide that has bound to it, e.g., via a covalent bond, to a electron transfer moiety (ETM) such as ferrocene. This is shown below in a portion of Fig. 30 from Blackburn. The oligonucleotide is detected by measuring electron transfer between the ETM, which is bound to an oligonucleotide, and the electrode - not between the surrounding medium and the electrode as suggested by the examiner. Detection of the oligonucleotide occurs because the ETM is brought into proximity to the electrode".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, as shown in above rejection and claims 1 and 2, since Blackburn *et al.*, teach that concatamer comprising at least one covalently attached ETM is attached to an electrode by hybridizing to a capture probe which is covalently attached to the electrode, the complex formed by the electrode, the concatamer and the capture probe is a complex formed by the sensing interface, the capture oligonucleotide, target oligonucleotide, and verification oligonucleotide as argued by applicant in top of page 9 of applicant's remarks. Since Blackburn *et al.*, teach detecting said ETM as an indicator of the presence of said target sequence (see column 141, claim 1) and insulators (such as resistance) is used to monitor electron transfer between ETM and the electrode (see column 92, fourth paragraph), and the measurement of insulators (such as resistance) must be performed in or through the hybridization buffer (ie., having ETM),

Blackburn *et al.*, disclose detecting the presence of said verification oligonucleotides (ie., the target sequence) on the sensing interface by measuring insulation of the sensing interface (ie., surface of the electrode) to interfacial electron transfer between the sensing interface and the surrounding medium (ie., the hybridization buffer containing ETM) as recited in (e) of claim 1. Second, the rejection is not based on Figure 30 of US Patent No.6,686,150 (see above rejection).

II. Related to the arguments in page 10, fifth paragraph bridging to page 11, third paragraph of applicant's remarks, the examiner has withdrawn the rejection under 35 U.S.C 102 (e) based on Durst *et al.*, in previous office action mailed on November 18, 2005.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Blackburn *et al.*, (January 29, 1998) as applied to claims 1, 2, and 48 above, and further in view of Lizardi *et al.*, (US Patent NO. 6,143, 495, filed on November 21, 1996).

The teachings of Blackburn *et al.*, have been summarized previously, *supra.* Blackburn *et al.*, teach that the size of RCP is designed such that it hybridizes "smoothly" to many capture probes on a surface (see column 25, lines 33-37).

Blackburn *et al.*, do not disclose that the stably hybridizing portions of the capturing and verification oligonucleotides are of about 12 nucleotides as recited in claim 3.

Lizardi *et al.*, teach that a region in a detection tag with 10-35 nucleotides forms a specific and stable hybridization complex with a detection probe (see column 10, second paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 3 wherein the stably hybridizing portions of the capturing and verification oligonucleotides are of about 12 nucleotides in view of patents of Blackburn *et al.*, and Lizardi *et al.* One having ordinary skill in the art has been motivated to do so because optimization of sizes of the stably hybridizing portions of the capturing and verification oligonucleotides, in the absence of convincing evidence to the contrary, would have been obvious to one having ordinary skill in the art at the time the invention was made. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to design the capturing and verification oligonucleotides wherein their stably hybridizing portions are about 12 nucleotides so that they hybridize "smoothly" to their corresponding capture probes on a surface and specific

and stable hybridization complexes would be formed. More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. Where the general conditions of a claim are disclosed in the prior art, it is not inventive, in the absence of an unexpected result, to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (MPEP 2144.05).

Response to Arguments

In page 11, fourth paragraph of applicant's remarks, applicant argues that "Blackburn does not disclose a method that includes 'measuring insulation of the sensing interface to interfacial electron transfer between the sensing interface and the surrounding medium' as required by claims 1 and 3. Lizardi et al. does not suggest such a method. Thus, Blackburn and Lizardi et al., no matter how combined, cannot render claim 3 obvious".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because Blackburn do teach a method that includes "measuring insulation of the sensing interface to interfacial electron transfer between the sensing interface and the surrounding medium" as required by claim 1 (see above Response to Arguments to the rejection under 35 U.S.C 102).

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Claims 4-8 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

July 31, 2006

FRANK LU
PRIMARY EXAMINER